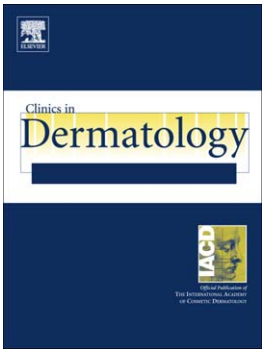
DOI:
10.1016/j.clindermatol.2016.02.004

Document Version
Peer reviewed version



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PII: S0738-081X(16)30019-0
DOI: doi: 10.1016/j.clindermatol.2016.02.004
Reference: CID 7016

To appear in: *Clinics in Dermatology*

Please cite this article as: Ovadia Caroline, Williamson Catherine, Intrahepatic Cholestasis of Pregnancy, *Clinics in Dermatology* (2016), doi: 10.1016/j.clindermatol.2016.02.004

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Key Words: intrahepatic cholestasis; obstetric cholestasis; pregnancy; etiopathogenesis; fetal risks; management

Word Count: 100 (*Abstract*) / 3,168 (*Text*) **Tables:** 1 **Figures:** 1 **Reference count:** 80

Conflicts of interest: none

Funding sources: Research that informed this review was funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St. Thomas and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR of the Department of Health.

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ABSTRACT

Intrahepatic cholestasis of pregnancy, also known as obstetric cholestasis, is a pruritic condition of pregnancy, characterized by an underlying elevation in circulating bile acids and liver derangement, and associated with adverse fetal outcomes, such as preterm labor and stillbirth. Limited understanding of the underlying pathophysiology and mechanisms involved in adverse outcomes has previously restricted treatment options and pregnancy management. Recent advances in these research fields provide tantalizing targets to improve the care of pregnant women affected by this condition.

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis, is a liver condition of pregnancy, characterized by pruritus and the biochemical finding of elevated serum bile acids, often in the presence of other signs of liver dysfunction. By definition, ICP is confined to pregnancy and the peripartum period and is diagnosed following exclusion of other etiologies for cholestasis. In addition to the maternal symptomatology, ICP can be associated with adverse fetal outcomes, such as spontaneous preterm birth, meconium staining of the amniotic fluid, and stillbirth;[1] hence, appropriate recognition and management are significiant.

The incidence of ICP varies dependent upon geographic location and ethnicity. For example, the incidence is 4% in Chile;[2] in the United Kingdom, it is 0.7%, but is higher in women of Indian or Pakistani origin,[3] while the incidence in China has recently been estimated at 1.2%, based on more than 100,000 hospital births.[4] Within the Californian population, genetic ancestry mapping has demonstrated higher levels of ICP in women of Native American ethnicity.[5]

ICP is more common in women with pre-existing hepatitis C and gallstone disease; hence, the benefit of serum screening and liver ultrasound in all women diagnosed with the condition.[6] Its incidence is also higher in women with multiple gestation pregnancies[7] and in those who conceived using assisted reproduction.[8]

Symptoms

The hallmark symptom of ICP is pruritus, i.e. "itching in the absence of a rash"; yet, scratching can often lead to secondary skin changes. Traditionally, pruritus is described on the palms and soles, but ICP-associated pruritus can be generalized.[9] Itching ranges from mild to a debilitating and intense symptom, and it is typically worse at night. Excoriated lesions (Figure) can become complicated by secondary infection. The onset of pruritus often precedes biochemical derangement.[10] making the diagnosis one to be considered in any woman with the characteristic itch in pregnancy.

Further symptoms relate to the effects of liver impairment. Bilirubin is elevated in approximately 10% of cases, and in this group jaundice can be detected (the condition was initially recognized as recurrent jaundice in pregnancy), and symptoms suggestive of malabsorption of fats, e.g. steatorrhea, can occur.[11] If there is evidence of malabsorption, impaired coagulation can occur, secondary to reduced vitamin K absorption, although this is not common, and a recent study into the coagulation parameters of 319 women with ICP did not demonstrate any women with abnormal coagulation parameters.[12]

Pruritus in Pregnancy and ICP

The cause of pruritus in ICP is not fully understood, although a number of possible pruritogens have been identified. It has long been established that bile acids can elicit itch, when applied to the skin,[13] and the lowering of serum bile acids with the use of ursodeoxycholic acid (UDCA) treatment for ICP is mirrored by a reduction in itch intensity.[14] There is some experimental evidence for a role of bile acids in pruritus as the secondary bile acid deoxycholic acid (DCA) has been shown to activate the G-protein coupled receptor, TGR5, on cutaneous afferent neurons, thereby eliciting a scratch response. The concentrations of DCA used for these experiments were much higher than are observed in women with ICP.[15] Also, the clinical relevance of this observation is not clear, as the pattern of bile acid levels and subjective itch intensity do not correlate well in ICP,[10] so bile acids alone are unlikely to cause pruritus in the disorder.

Lysophosphatidic acid (LPA) is a potent pruritogen[16] that is produced from lysophosphatidyl choline by the action of the enzyme autotaxin. Autotaxin activity is elevated in the serum of patients with pruritic cholestatic conditions,[17] and it is higher in women with ICP than with other liver-associated disorders of pregnancy.[18] Genetic variants of the enzyme adiponutrin (PNPLA3) have been found in women with ICP; this enzyme is expressed in the liver and skin, and catalyses the breakdown of LPA.[19]

Progesterone, which rises during pregnancy, is destined for excretion in part by conjugation with a sulfate group, which renders the hormone more soluble. Sulfated metabolites of progesterone are elevated in ICP compared with normal pregnancy,[20] and of these, 5β-pregnan-3α-20α-diol-sulfate (PM3S) is directly associated with the level of pruritus experienced by the patient.[21] PM3S has been demonstrated to signal via TGR5 in a cell line, when exposed to PM3S at the physiologic

concentrations found in the serum of women with ICP. It has triggered a scratch response, when administered to mice intradermally.[21] LPA and PM3S are the likely candidates to be the pruritogens in ICP.

Etiology

Maternal disease

The etiology of ICP is influenced by a combination of genetic, endocrine ,and environmental factors. Evidence for a genetic etiology includes an increased risk in first degree relatives,[22] the presence of mutations in biliary transporters, e.g. the Bile Salt Export Pump (BSEP/ABCB11) and Multi-Drug Resistance protein 3 (MDR3/ABCB4),[23, 24] and polymorphisms that confer susceptibility in these genes and the principal nuclear receptor that influences bile acid homeostasis, Farnesoid X Receptor (FXR).[25] By definition, women with ICP are not typically cholestatic outside of pregnancy. As such, it has been proposed that the onset in pregnancy could relate to epigenetic changes. In support of this, altered DNA methylation in the promoter regions of FXR and another nuclear receptor, pregnane X receptor (PXR), has been demonstrated in women with ICP, compared to normal pregnancies, although the functional relevance of this has not yet been determined.[26]

Another potential explanation for the onset of ICP in pregnancy is the altered gestational endocrine environment. Onset is most common in the third trimester, when circulating estrogen and progesterone are reaching their peak, and thus it is unsurprising that elevated serum concentrations of metabolites of both hormones have been associated with ICP. Indeed, some women with a history of ICP develop pruritus on consumption of the combined oral contraceptive pill.[27] Signalling via the estrogen receptor ERα, 17β-estradiol can impair the induction of BSEP expression by bile acid-liganded FXR in a mouse model[28] and human cell line.[29] In addition to their association with

pruritus, sulfated progesterone metabolites can impair bile acid influx into[30] and efflux from[31] the hepatocyte, and partially antagonise FXR,[32] all of which can exacerbate cholestasis.

Environmental factors have been proposed for influencing the etiology of ICP. Epidemiologic studies have shown an increased prevalence of the disorder in the winter months,[33] with low maternal vitamin D levels or reduced dietary selenium intake being proposed as plausible contributors. Selenium intake from food varies throughout the yea,r and there is reduced sun exposure in the winter. ICP also occurs more commonly in patients with reactive hepatitis C serology.[34]

Fetal disease

Several recent studies have evaluated the relationship between adverse pregnancy outcome and biochemical derangements in women with ICP. The two largest prospective cohort studies, and several smaller series, have demonstrated that elevated maternal serum bile acid concentrations (i.e. ≥40 μmol/L) are associated with increased rates of spontaneous and iatrogenic preterm labor, meconium-stained amniotic fluid, fetal hypoxia and, in the largest study, stillbirth.[1, 35-38] This observation suggests that bile acids may also be elevated in the fetal/placental circulation and that this results in complications, but the specific mechanisms have not been fully elucidated. The stillbirths suffered by women with ICP are unpredictable and occur in normally grown fetuses without evidence of chronic placental insufficiency.[39] In view of this, a number of theories exist as to a sudden catastrophic cause of the stillbirth. Abnormal placental vascular responses have been suggested as a possible cause, with sudden vasospasm potentially responsible for fetal death; in support of this the bile acid taurocholate, which is markedly elevated in ICP, impaired placental arterial vascular pressure elevation in an *ex vivo* model.[40]

Bile acids have also been found to impair fetal cardiomyocyte function *in vitro*,[41] and thus a sudden cardiac arrhythmia has been suggested as a possible cause of the intrauterine death. Fetal echocardiography demonstrated significantly different findings with regard to velocities at the mitral and tricuspid valves in fetuses of women with "severe" ICP (total bile acids >40 μmol/l) compared with women with lower bile acid levels or normal pregnancies,[42] and differences were seen in myocardial performance indices[43] and myocardial deformation,[44] although the clinical implications of these findings have yet to be elucidated.

IBile acids may affect neonatal respiratory function, as elevated bile acids have been found in the bronchioalveolar lavage fluid from neonates born from pregnancies complicated by ICP, which was not observed in those born from control pregnancies.[45] This may affect the outcome of babies born to such pregnancies, as bile acids reduce lung surfactant in a rat model of cholestatic pregnancy, by acting on macrophages via TGR5 to induce the action of phospholipase A2 which degrades surfactant.[46] In another rat model they were found to affect respiratory parameters by signalling via FXR at the hypoglossal nerve.[47]

Management

The drugs for which placebo-controlled studies have been performed in the treatment of ICP are summarized in Table. Ursodeoxycholic acid (UDCA) has the most experimental data to support its use. It is a hydrophilic bile acid that improves bile acid profiles in cholestatic liver disorders via multiple mechanisms, including enhanced biliary excretion (reviewed by Lazaridis[48]). It also reduces the extent of the elevation of fetal bile acids in ICP.[49] UDCA is the most widely prescribed pharmacologic treatment for ICP, although the most recent Cochrane review (2013) was still not able to recommend its use for ICP for fetal benefit based on existing evidence.[50] Subsequently, a

number of further trials have been undertaken, and the most recent meta-analyses of these demonstrated that UDCA improves biochemical parameters and pruritus intensity.[51, 52] Whilst the large PITCH study showed benefit in itch scoring on a Visual Analogue Scale, it was by a smaller degree than that predetermined as necessary for worthwhile symptomatic benefit by patients and practitioners.[14] The impact of UDCA treatment on fetal and neonatal outcomes has not been evaluated with an adequately powered study, although the Phase II PITCHES clinical trial commencing this year in the UK will aim to address this. A meta-analysis of all trials that compared UDCA to another treatment demonstrated that its use reduces the likelihood of adverse pregnancy outcomes, but this study was limited by relatively small numbers of direct comparisons of UDCA with placebo.[51] Interestingly, UDCA was shown to improve the fetal bile acid profile in umbilical cord blood, with up-regulation of placental expression of the export pump ATP-binding cassette (ABC)G2 providing a potential explanation for enhancement of fetal bile acid excretion across the placenta.[53] Additionally, UDCA was able to reverse the arrhythmogenic effect of taurocholic acid in an *in vitro* rat model of the fetal heart.[54]

S-adenosyl-L-methionine (SAMe) is required for phospholipid biosynthesis, hence is thought to be hepatoprotective in ICP. Small studies in ICP have demonstrated conflicting results, therefore there is not reliable evidence upon which to recommend clinical benefit. Additionally, the requirement for daily intravenous infusion precludes practical and patient-acceptable administration for many women with ICP. Activated charcoal, guar gum,and cholestyramine have been tried, based on their ability to prevent of intestinal bile acid resorption; a single study with activated charcoal showed a tantalising improvement in biochemistry, but the small size of this trial has not justified its clinical use. Results for cholestyramine and guar gum have been fairly equivocal, with no evidence that they out-perform UDCA, and concern regarding impairment of fat-soluble vitamin intake associated with cholestyramine preclude its routine use in pregnancy. Dexamethasone has been used, as it inhibits

adrenal production of estrogen precursors, thus lowering placental estrogen production. Results of a single study were not significant and concerns regarding recurrent glucocorticoid use in pregnancy (i.e. risks of maternal impaired glucose tolerance and childhood behavioral effects) have deterred many clinicians from its use.

Rifampicin has been used in combination with UDCA for women with severe and resistant disease to monotherapy with UDCA alone. Rifampicin is a PXR agonist, thus works via a different and synergistic mechanism to reduce serum bile acids. It is successful in reducing total serum bile acids and pruritus in around 50% of women with ICP.[55] Interestingly, rifampicin has been shown to reduce autotaxin expression in cell lines, which could explain its mechanism in improving pruritus.[17]

Aqueous cream with 1 or 2% menthol diminishes th pruritus in some women, and vitamin K treatment may reduce the risk of peripartum haemorrhage in women with steatorrhoea, who are at risk of vitamin K malabsorption.

Women with ICP are often admitted to the hospital for regular fetal surveillance, for example with fetal movement chart completion, cardiotocography, biophysical profiling, ultrasound of growth parameters,and Doppler flow velocimetry; yet, evidence for the value of these tests has not been established. Even where differences in recorded values are obtained from the normal population (e.g. umbilical artery Doppler measures),[56] using these to predict fetuses at risk of adverse outcomes has been elusive.

Delivery is often expedited in women with ICP due to concerns about the risk of adverse pregnancy outcomes, although international consensus as to the optimal gestation week for deliver has not been reached. Typically, the balance of risk versus implications of preterm delivery has resulted in labour being induced around 37-38 gestational weeks. Interestingly, two recent studies using different experimental approaches have suggested that delivery around 36 weeks' gestation may be associated with the best outcomes. Using a Californian cohort of pregnant women and fetal/neonatal mortality data, the risk of death was found to be lower with delivery at 36 weeks than expectant management for women with ICP (perinatal mortality 4.7 *vs*. 19.2 per 10,000).[57] In the second study, morbidity in addition to mortality were considered in terms of quality adjusted life years (QALYs) with a decision-analysis model, which also found that delivery at 36 weeks would give the best outcomes.[58] How this affects clinical decisions remains to be determined, given increasing evidence of the negative effects of delivery at earlier gestations on intellectual development[59] (even at 37-40 weeks' gestation). Evidence regarding induction of labor for women with ICP does not indicate any increased risk of emergency caesarean section or fetal asphyxia (determined by Apgar score <7 at 5 minutes).[60]

Associated Conditions

Bile acids have traditionally been viewed as detergent molecules that aid digestion of fats, secondary to their hydrophobic properties; owever, they have important roles in metabolism, with multiple signalling effects on downstream organs, such as the pancreas and adipose tissue. The two major bile acid receptors currently recognized are the nuclear receptor FXR and the G-protein coupled cell surface receptor TGR5. Bile acids binding of these receptors results in multiple downstream metabolic effects on glucose and lipid metabolism. In view of the elevated bile acids found in ICP, it is unsurprising that it is not simply a condition limited to liver impairment and adverse fetal outcomes. A number of studies, using different methodologies and patient demographics, have

demonstrated that women with ICP are at a greater risk of developing gestational diabetes mellitus (GDM),[61, 62] dyslipidemia, and proportionately larger babies than women with uncomplicated pregnancies.[63] Mouse models have also demonstrated that the girls of cholestatic pregnancies also develop impaired glucose tolerance when challenged with a Western diet,[64] and the 16-year-old children of ICP pregnancies had dyslipidemia, higher BMI and waist / hip girth measurements compared with the children of uncomplicated pregnancies. Six-month-old offspring of cholestatic rat pregnancies demonstrated altered hypothalamic neuropeptide Y and proopiomelanocortin levels, suggesting a mechanism for appetite stimulation in the offspring of cholestatic pregnancies.[65]

ICP has been associated with the subsequent onset of pre-eclampsia in a retrospective study that compared 78 women with ICP to 300 healthy pregnant women.[66] For women entered into the Swedish Medical Birth Register between 1997 and 2009, women with ICP had an adjusted odds ratio 2.62 (95% CI 2.32-2.78) of also having pre-eclampsia in pregnancy.[62] The mechanism for this association has not been determined.

Long-term Implications

Women with ICP have slightly higher long term risks of cancer of the liver and biliary tree (HR 3.61; 95% CI 1.68-7.77, and 2.62; 95% CI 1.26-5.46, respectively),[67] as well as higher rates of other hepatobiliary diseases, most commonly cholelithiasis.[6] In addition, a Swedish population-based study using national disease databases also found mildly elevated rates of diabetes mellitus, thyroid disease, psoriasis, inflammatory polyarthropathies, Crohn's disease, and cardiovascular disease.[67] Women with ICP were found to have altered P-wave characteristics on electrocardiography compared with women with normal pregnancies,[68] and women with severe ICP had significantly

altered QT intervals on ECG compared to those with mild disease or normal pregnancies,[69] perhaps reflecting this long-term cardiovascular risk.

Future Directions

As further insights are gained into the etiology of ICP, improvements in the management of patients affected by the condition become possible. Understanding the underlying pathophysiology will certainly enable us to:

- Develop predictive biomarkers enabling targeted obstetric care to women at risk of developing ICP from early pregnancy on. Putative biomarkers, such as autotaxin[18] and the sulphated progesterone metabolites,[21] have been suggested and are promising for future larger-scale studies.
- Improve diagnostic testing to determine which women symptomatic of pruritus in pregnancy have ICP, and which are suffering from benign gestational pruritus (estimated to occur in 25% of pregnancies).[9] Identifying alternative diagnostic markers to total serum bile acids will also alleviate the confusion caused by the postprandial elevation seen in bile acids, differing diagnostic methodology (enzymatic, liquid chromatography mass spectrometry) and interlaboratory reference ranges.
- Determine which ICP pregnancies are associated with adverse fetal outcomes – currently, the term “severe” ICP is used for women with bile acids >40 μmol/L. Several studies have demonstrated associations between elevations in serum bile acid or earlier disease onset and adverse outcome;[1, 35-38] however, it is currently impossible to predict which of these more “at risk” pregnancies will have adverse outcomes.
- Prevent disease onset - both in terms of prevention of cholestasis, perhaps by enhancing bile acid excretion from the hepatocyte and impairing its gastrointestinal reuptake, or by

reducing endogenous bile acid production, as well prevention of the consequences of cholestasis, such as protection of the hepatocyte from the toxic build-up of bile acids, prevention of pruritogen production, avoidance of development of metabolic disturbances such as dyslipidemia and GDM, and reduction of bile acid transplacental transfer to the fetus.

- Manage the condition - in terms of improvements in circulating bile acid profile, targeting the cause of pruritus (pruritogens or pathways), reducing adverse pregnancy outcomes and optimising timing of delivery. The development of pharmacological treatments targeting the bile acid receptors FXR and TGR5 provide novel agents with therapeutic potential for ICP. Giving drugs with potential widespread metabolic implications to pregnant women should be undertaken with great caution.
- Identify and address long-term health implications – by understanding how ICP is linked to future health problems for mothers and offspring to whom specific therapeutic interventions can be targeted.

Research to elucidate the etiology of ICP is likely to uncover metabolic factors of relevance to other diseases, which is an enticing prospect given the increasing pandemic of diabetes, obesity, and related diseases.

Table. Summary of evidence for pharmacologic treatments used in ICP.

Drug	Numbers in treatment group	Improved biochemistry with drug	Improved pruritus with drug	Improved fetal outcome with drug	Reference
UDCA	8	Total bile acids, ALT, bilirubin significant p<0.001	Significant p<0.001	Later delivery significant p<0.05	Diaferia, 1996[70]
	8	Bilirubin, AST, ALT significant p<0.05	Significant p<0.02	Later delivery significant p<0.01	Palma, 1997[71]
	47	ALT, bilirubin significant p<0.01 *In subgroup with bile acids ≥40µmol/L (n=12), significant reduction in ALT and total bile acids*	Not significant *In subgroup with bile acids ≥40µmol/L (n=12), significant reduction in pruritus*	Not significant; 12/47 preterm birth	Glantz, 2005[72]
	34	Total bile acids, ALT significant p<0.05	Significant p<0.05	Preterm delivery, intrapartum fetal distress, MSAF and neonatal asphyxia all p<0.05	Liu, 2006[73]
	56	ALT, GGT, bilirubin significant p<0.01	Not significant p=0.11 *In women with raised serum bile acids there was a significant reduction in pruritus*	MSAF significant p<0.05	Chappell, 2012[14]

	9	Not significant	Significant p<0.05	Not significant	Joutsiniemi 2014[74]
SAMe	6	Bilirubin, ALT, total bile acids significant p<0.05	"High dose" significant p<0.01	Not reported	Frezza, 1984[75]
	15	Significant p<0.01	Significant, p value not given	Not significant	Frezza, 1990[76]
	9	Not significant	Not significant	Not significant	Ribalta, 1991[77]
Activated charcoal	10	Significant p<0.05	No difference	No difference	Kaaja, 1994[78]
Guar gum	19	Statistical comparison with placebo not presented	Patient-assessed, but not investigator-assessed, pruritus significant p<0.05	No effect detailed	Riikonen, 2000[79]
Cholestyramine	42	9/42 - AST, ALT, 8/42 – total bile acids improved; UDCA significantly better p<0.02	8/42 reduction in pruritus score by 50%. UDCA significantly better p<0.001	5/42 preterm birth, lower Apgar score than UDCA group p<0.05	Kondrackiene, 2005[80]* Compared with UDCA
Dexamethasone	36	Not significant	Not significant	Not significant	Glantz, 2005[72]
Rifampicin	27	14/27 (54%) improved bile acids	10/15 reported improved pruritus	25/27 had adverse neonatal outcomes (mainly prematurity	Geenes, 2015[55]* Observational

				23/27)	study

UDCA, ursodeoxycholic acid; ALT, alanine transaminase; AST, aspartate transaminase; MSAF, meconium-stained amniotic fluid; GGT, gamma-glutamyl transferase; SAMe, S-adenosyl-L-methionine.

Results are shown from publications in the English language available by PubMed searching, comparing drug with placebo, unless otherwise indicated where no placebo-controlled study has yet been performed.

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Figure legend

Figure. Excoriated skin lesions in patients with ICP. (A) mild, early skin changes, and (B) appearance of skin lesions following prolonged scratching (Fig. 1A donated by Dr. George Kroumpouzos, and Fig. 1B is used with permission of Jenny Chambers, *ICP Support*, Sutton Coldfield, England).

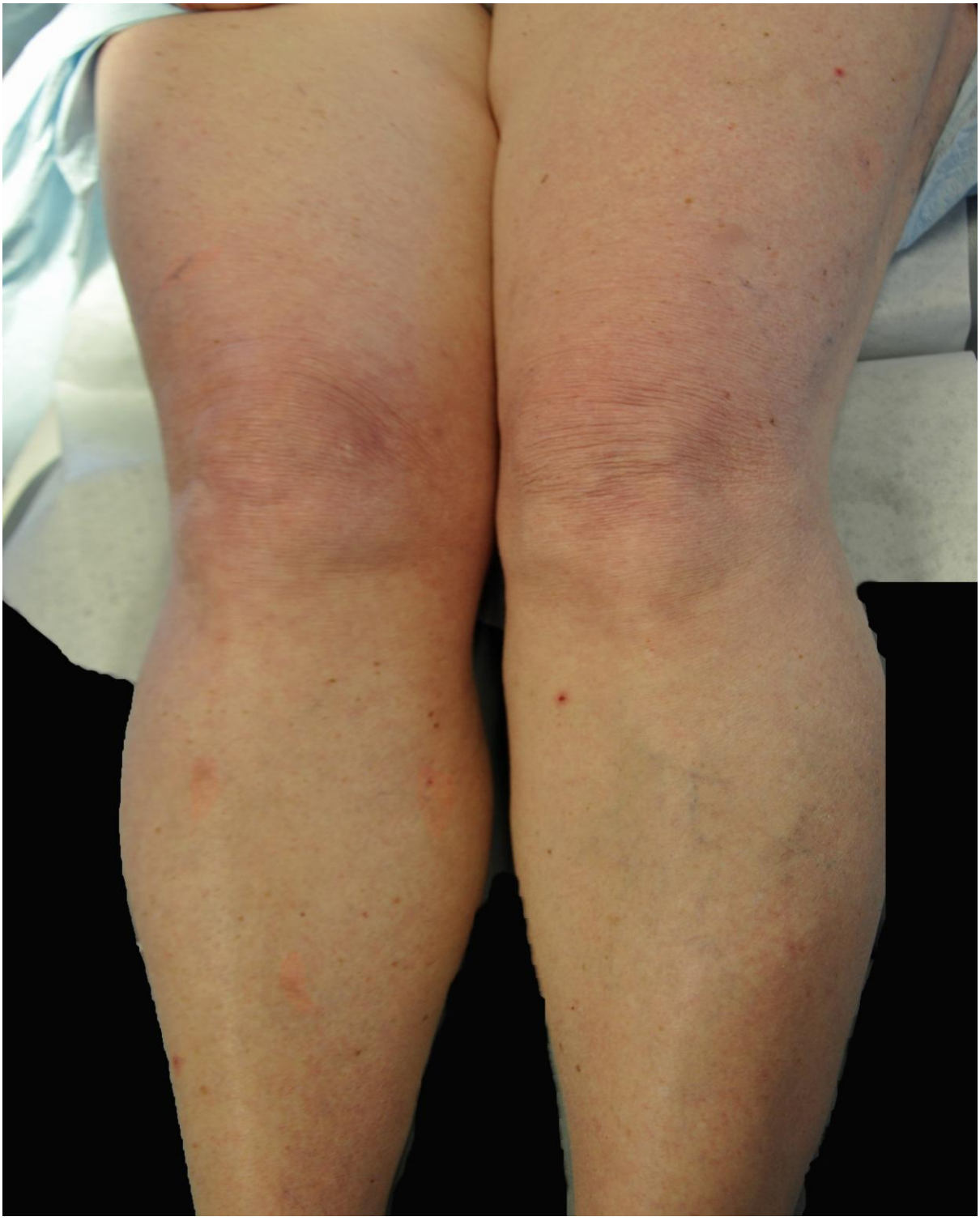

Figure 1A

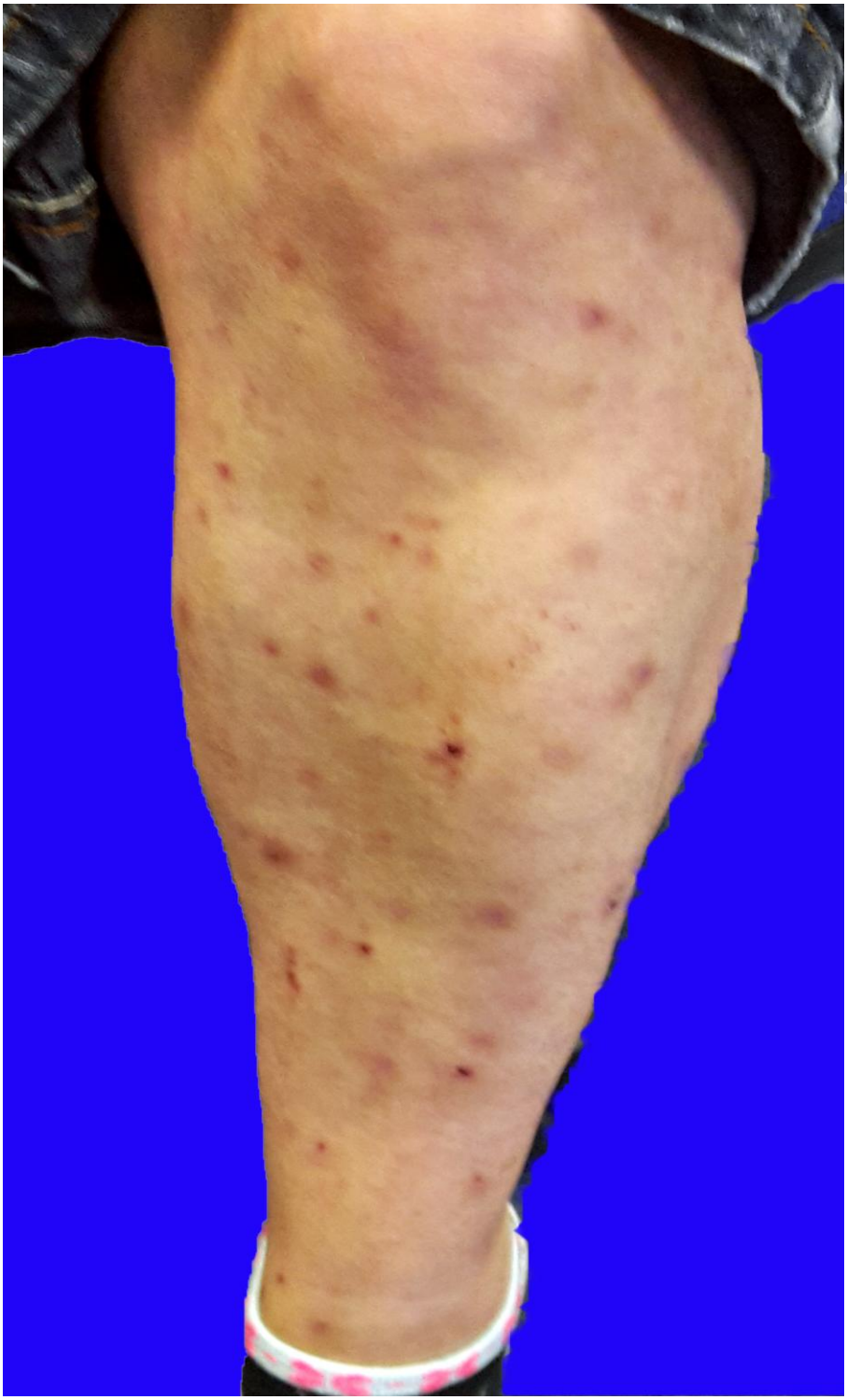

Figure 1B